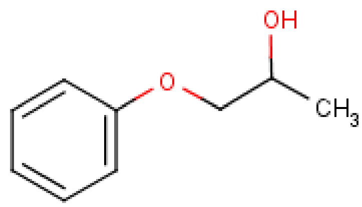
Propylene Glycol Phenyl Ether

(CAS# 770-35-4)

(Synonyms: 1-Phenoxy-propan-2-ol; 1-Phenoxy-2-propanol; Phenoxyisopropanol; Propylene phenoxetol; 2-Phenoxy-1-methylethanol; 2-Propanol, 1-phenoxy-; PPh)



Propylene Glycol Phenyl Ether Acute REL

Reference Exposure Level	**6.3 mg/m^3 (1 ppm)** [based on oral study]
Critical effects	Fetotoxicity
Hazard Index target	Skeletal system

Propylene Glycol Phenyl Ether 8-hour REL

Reference Exposure Level	**6.3 mg/m^3 (1 ppm)** [based on oral study]
Critical effects	Fetotoxicity
Hazard Index target	Skeletal system

1 Physical and Chemical Properties

Physical form	clear, colorless liquid at room temperature
Structural formula	$(C_6H_5)OCH_2CH(OH)CH_3$
Molecular weight	152.19 g/mole
Density	1.059 g/cm^3
Boiling point	242.7 ºC
Melting point	11.4 ºC
Vapor pressure	0.022 mm Hg @ 25ºC
Flash point	129 ºC
Log K_{OW}	1.50
Water solubility	11,000 mg/L @ 25ºC
Atmospheric half-life	3.45 hrs
Conversion factor	1 ppm = 6.22 mg/m^3

2 Production, Use, and Exposure

Propylene glycol ethers are manufactured by the reaction of propylene oxide with methyl alcohol or n-butyl alcohol. Chain lengths of the products will vary depending on the molar ratio of reactants, the temperature, and the pressure used for the reaction. Monopropylene glycol ethers result from lower molar ratios of propylene oxide to alcohol and milder conditions, whereas increases in propylene oxide, temperatures, and pressures will produce di- and tripropylene glycol mono-alkyl ethers (OECD 2003). The estimated production of propylene glycol phenyl ether (PPh) in 2004 was 18 million pounds (SRI International, 2000, cited in OECD 2004).

Commercial PPh has a minimum purity of 93%, with 1-phenoxy-propan-2-ol (the alpha isomer) comprising > 85% of the mixture and 2-phenoxy-propan-1-ol (the beta isomer) comprising < 15%. The remaining 7% consists of up to 7% di-PPh, 0.1% phenol, and 0.35% water. PPh is primarily used as a solvent to facilitate the mixing of organic and aqueous constituents in paints, coatings, and films. Other uses for PPh include: latex coalescent in water-based architectural and industrial coatings and adhesives; carrier solvent for textile dyes; solvent for ink in ball point and felt tip pens, stamp pads, and textile printing pastes; and paint remover. PPh is also used in cosmetics and soaps for its antibacterial properties (OECD 2004).

The hazardous properties of the reactant propylene oxide necessitate the use of enclosed equipment during manufacture, thereby limiting worker exposure at this point. The greatest exposure potential exists for commercial workers and other consumers, most likely via inhalation or dermal contact, when coatings are applied to surfaces or when liquid products containing PPh are otherwise used. Exposure to the general population is also possible through inhalation of ambient air containing PPh released from industrial processes or through evaporation of coatings or other products containing PPh. The estimated soil/water-sediment/water partition coefficient for PPh (K_{OC} = 19) suggests that it has high soil mobility and can leach from soil deposits to groundwater, thereby allowing possible exposure through ingestion of drinking water (OECD 2004).

3 Pharmacokinetics and Metabolism

There are 3 major routes of metabolism for PPh. The first involves cleavage by O-dealkylation to yield propylene glycol and phenol, followed by sulfate or glutathione conjugation of phenol and excretion in urine. The second is direct conjugation of PPh with sulfate or glucuronide and subsequent excretion in urine. The third metabolic route involves the ring hydroxylation of PPh or its oxidized propanone metabolite, followed by sulfate conjugation and excretion in urine (OECD 2004).

PPh has been shown to be absorbed rapidly from the gastrointestinal tract and excreted. Saghir et al. (2003) exposed adult male Fischer 344 rats to single oral doses of 10 mg/kg and 100 mg/kg body weight ^{14}C-PPh and collected urine at 0-12, 12-24, and 24-48 hrs and feces 0-24 and 24-48 hrs post-dosing. More than 80% of the administered radioactivity was excreted in urine within 12 hrs and greater than 93% of either dose was excreted by 48 hrs. Between 6 and 8% of both doses of PPh were excreted in the feces within 48 hours, with the majority being excreted within 24 hrs. Metabolites identified in urine included sulfate and glutathione conjugates of phenol, low levels of hydroquinone, sulfate and glucuronide conjugates of the parent compound, and a ring-hydroxylated metabolite of PPh (Saghir et al. 2003).

4 Acute Toxicity

A nose-only inhalation study by Gamer et al. (1991, unpublished report cited in OECD 2004) demonstrated no deaths when Wistar rats were exposed to a single dose of 5400 mg/m^3 Protectol PP (commercial isomeric PPh mixture) for 4 hours. All subjects exhibited unspecified clinical abnormalities, including breathing difficulties, on the day of exposure, but no symptoms were observed thereafter. The LC_{50} was determined as > 5400 mg/m^3 (870 ppm).

Kirsch and Hildebrand (1987, unpublished report cited in OECD 2004) administered single oral gavage doses of 1000 or 2000 mg/kg PPh in an olive oil vehicle to Wistar rats (5/sex/group) and observed the animals for 14 days. One male rat from the high dose group died on day 1 but all the remaining animals survived the observation period. Rats from both dose groups were in poor general state, exhibiting dyspnea and apathy. Rats in the high dose group also exhibited abnormal stance, staggering, atonia, paresis, absence of pain reflex, absence of corneal reflex, piloerection, and dehydration. At the end of the 14-day observation, necropsy of the 19 surviving animals showed no grossly observable lesions. The oral LD_{50} was indicated as > 2000 mg/kg in rats.

5 Derivation of Acute REL (1-hour exposure)

Study	Hellwig and Hildebrand 1995
Study population	Himalayan rabbits
Exposure method	Oral gavage
Exposure continuity	Once daily
Exposure duration	Gestational days 7-19
Critical effects	Increased fetal skeletal variations (13th rib)
LOAEL	540 mg/kg-d
NOAEL	180 mg/kg-d
LOAEL uncertainty factor (UF_L)	1 (NOAEL observed)
Subchronic uncertainty factor	1 (not applicable for an acute REL)
Interspecies Uncertainty Factor	
Toxicokinetic (UF_{A-k})	√10 (default for oral study)
Toxicodynamic (UF_{A-d})	√10
Intraspecies Uncertainty Factor	
Toxicokinetic (UF_{H-k})	√10
Toxicodynamic (UF_{H-d})	√10
Cumulative uncertainty factor	100
Oral dose	1.8 mg/kg-d
Route-to-route extrapolation factor	70 kg/20 m^3/d
Acute Reference Exposure Level	**6.3 mg/m^3** (1.8 mg/kg-d*3.5 kg/m^3-d)

This acute REL is based on a study by Hellwig and Hildebrand (1995, cited in OECD 2004) in which pregnant Himalayan rabbits (15 dams/group) were administered 0, 60, 180, or 540 mg/kg-d PPh by oral gavage from gestation days 7 through 19. The study established a LOAEL of 540 mg/kg-d based on decreases in maternal weight gain, maternal apathy, and increased skeletal variations in the offspring. Developmental toxicity, unlike subchronic and chronic toxicity, can occur in a small window of time during a critical stage of development. Therefore, there is no duration adjustment when extrapolating from a longer exposure duration per day down to a one-hour exposure. Default values of $\sqrt{10}$ are used for interspecies toxicokinetic and toxicodynamic variability between rabbits and humans. Since one of the endpoints involves a sensitive subgroup (fetuses), the default intraspecies toxicokinetic uncertainty factor of $\sqrt{10}$ is applied and a default toxicodynamic uncertainty factor of $\sqrt{10}$ is used in the absence of data to indicate otherwise. In converting the oral dose to an air concentration, it is assumed that the efficiency of PPh absorption is the same between an oral dose and inhalation. The route-to-route conversion factor assumes that a 70 kg adult male breathes 20 m^3 air/d. The resultant REL is therefore the oral dose multiplied by the route-to-route extrapolation factor and by the chronic to acute adjustment.

6 Derivation of 8-Hour REL

The study by Hellwig and Hildebrand (1995, cited in OECD 2004) is also used for the derivation of an 8-hour REL, which in this case has the same value as the acute REL. Since developmental toxicity can occur within a narrow window of minutes or hours during a critical stage of development, no duration adjustment is needed for extrapolation to an 8-hour duration. Furthermore, since the fetotoxicity endpoint is a function of exposure only during gestation and PPh is non-accumulating, the exposure is considered chronic for the fetus and an uncertainty factor to account for differences between subchronic and chronic exposures is not applied. Therefore, the 8-hour and acute RELs have the same value.

7 Other Toxicity

Dermal Exposure

Since exposure can occur via dermal contact through the use of products containing PPh, a brief summary of toxicity studies involving dermal exposure is included. Calhoun et al. (1986, unpublished report cited in OECD 2004) applied 0, 100, 300, or 1000 mg PPh/kg body weight to the clipped dorsal skin of New Zealand white rabbits for 6 hrs/day, 5 days/week, over a period of 4 weeks (total of 19 applications). Over the course of the study, the animals were monitored for clinical signs of toxicity, body weight changes, hematological and clinical chemistry, and urinalysis changes. Organ weights, gross and microscopic pathology were examined at autopsy. All rabbits survived treatment with no changes in body weights and no overt signs of systemic toxicity. All subjects showed some dermal irritation characterized by varying degrees of hyperemia and exfoliation, depending on the dose. Except for skin at the site of application, histopathological examination revealed no adverse effects related to PPh treatment when high dose subjects were compared to controls. The study established a NOAEL of 1000 mg/kg-day for systemic toxicity, whereas the NOAEL for local effects on the skin was <100 mg/kg. This study also determined that there was no toxicity, via dermal exposure, to reproductive organs based on organ weights, gross observation, or microscopic examination.

Phillips et al. (1985, unpublished report cited in OECD 2004) applied 1000 mg PPh/kg body weight to the clipped dorsal skin of 10 female New Zealand white rabbits for 24 hrs/day over the course of 14 consecutive days. Erythema and exfoliation were observed in all rabbits. No effects on survival, body weights, urinalysis, organ weights, or gross pathology were observed. The NOAEL for systemic toxicity was established as 1000 mg/kg body weight.

Reproductive and Developmental Toxicity
BASF Corporation (2000, unpublished report cited in OECD 2004) conducted a two-generation toxicity test in which 0, 100, 1000, or 5000 ppm (0, 11.3, 113.9, 477.5 mg/kg bw/day) PPh were administered in the drinking water to two generations of Wistar rats (25/sex/group) over an average of 26 weeks in parental generations. First generation rats (F0) received PPh 77 days prior to mating while the second parental generation (F1) received PPh for their lifetimes until termination. F0 and F1 reproductive performance were not affected at any dose. Estrous cycle, mating behavior, conception, gestation, parturition, lactation and weaning, as well as sperm parameters and sexual organ weights, and gross and histopathological findings of these organs were similar between control and treated animals. Signs of general systemic toxicity, characterized by decreased water and food consumption and decreased body weight and body weight gain were noted in F0 and F1 animals receiving the highest dose although pathology and histopathology did not reveal substance-related adverse effects. Pups of F0 and F1 parents receiving 5000 ppm PPh exhibited signs of developmental toxicity in terms of reduced body weight and body weight gain and delayed sexual maturation. NOAELs established in this study are as follows: reproductive performance and fertility NOAEL = 5000 ppm for F0 and F1 parents; developmental toxicity NOAEL = 1000 ppm for F1 and F2 progeny; general systemic toxicity NOAEL = 1000 ppm for F0 and F1 parents.

The following study by Hellwig and Hildebrand (1995, cited in OECD 2004) is in agreement with the BASF study above in demonstrating that PPh confers developmental toxicity at high doses that also produce toxicity in the dam.

Route of Exposure Species, Dose/Exposure Levels	**Results: Maternal Tox. (NOAEL, LOAEL)**	**Results: Offspring (NOAEL, LOAEL)**
Oral (gavage) Himalayan rabbit 0, 60, 180, 540 mg/kg-d Gestation days 7 through 19	No effects at 0, 60, or 180 Decreased weight gain, apathy at 540 mg/kg-d NOAEL = 180 mg/kg-d LOAEL = 540 mg/kg-d	No effects at 0, 60, or 180 Increased skeletal variation (13^{th} rib) at 540 mg/kg-d NOAEL = 180 mg/kg-d LOAEL = 540 mg/kg-d

Table adapted from OECD 2004.

8 Environmental Fate

The EPIWIN/APO model (U.S. EPA) estimates that the atmospheric photodegradation half-life of PPh is 3.45 hours, based on 12 hours of sunlight/day and an average hydroxyl radical concentration of 1.5×10^6 OH/cm^3. The ether linkages of propylene glycol ethers are not expected to easily hydrolyze, therefore the ether groups are generally stable in water under neutral conditions at ambient temperatures. The estimated Henry's Law Constant of 4.36×10^{-7} $atm\text{-}m^3$/mole for PPh indicates that it has limited potential to partition from water to air. The environmental distribution of PPh, as predicted by Mackay Level III fugacity modeling, is 1.03%

in air, 46.6% in water, 52.3% in soil, and 0.104% in sediment. PPh was “readily biodegradable” by all criteria in a biodegradation study measuring oxygen depletion, CO_2 production, and organic carbon depletion (OECD 301F). When incubated with three soil types for 25 days, PPh degraded rapidly under aerobic conditions, reaching 50% removal within 1 to 7 days, but degraded very little under anaerobic conditions. With a predicted bioconcentration factor of 0.776 and Log K_{OW} of 1.50, PPh has very limited potential to bioaccumulate. PPh is therefore unlikely to persist in the environment (OECD 2004).

9 References

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